REMARKS

The June 4, 2007, Official Action and the references cited therein have been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set forth in the June 4, 2007, Official Action. Therefore, the initial due date for response was September 4, 2007. A petition for a three (3) month extension of time is presented with this response, which is being filed within the three month extension period.

The Examiner has rejected claims 91-95, 97-101, 103-107, 109-111, and 113 under 35 U.S.C. §112, second paragraph for alleged indefiniteness.

Claims 91-95, 97-101, 103-107, 109-111, and 113 stand rejected under 35 U.S.C. §112, first paragraph for allegedly failing to satisfy the written description and enablement requirements of the statute.

The Examiner has rejected claims 91, 92, 95, 96, 98, 104, and 110-114 under 35 U.S.C. §102(a) as allegedly anticipated by Hu et al. (Clin. Cancer Res. (2000) 6:880-886) as evidenced by Jiang et al. (PNAS (2002) 1749-1753).

Claims 91, 95, and 110 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Schultz et al. (Anticancer Res. (1995) 15:1135-1139) as evidenced by Oikawa et al. (Eur. J. Pharm. (1996) 318:93-96).

The Examiner has also rejected claims 91-94 and 98-100 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,783,760 as evidenced by Stambolic et al. (Cell (1998) 95:29-39).

Lastly, claims 91, 92, 95, 96, 101, 102, 104, and 110-114 have been rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over

claims 1-3 of U.S. Patent No. 6,777,439. Applicant submit herewith a Terminal Disclaimer and, as a result, any patent granted on the present application would expire on the same date that the '439 patent expires. Applicant respectfully submits that the nonstatutory obviousness-type double patenting rejection has been overcome and requests its withdrawal.

In accordance with the instant amendment, Applicants have cancelled claims 95, 97, 101, 103, 107, 109, 113, and 114 and added new claims 120 and 121. Support for new claims 120 and 121 can be found for example, at page 4, lines 15-27; page 5, lines 12-14; page 14, lines 10-15; page 78, lines 9-33; and Figure 16. No new matter has been introduced into this application by reason of any of the amendments presented herewith.

The foregoing rejections constitute all of the grounds set forth in the June 4, 2007, Official Action for refusing the present application. Applicants respectfully request reconsideration and examination of this application and the timely allowance of the pending claims in view of the amendments and arguments set forth below.

CLAIMS 91-95, 97-101, 103-107, 109-111, AND 113, AS AMENDED, SATISFY THE REQUIREMENTS OF 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner has rejected claims 91-95, 97-101, 103-107, 109-111, and 113 under 35 U.S.C. §112, second paragraph for alleged indefiniteness. Specifically, the Examiner is unclear whether there is any difference in scope of the recitations "PTEN agonist" and "PI3 kinase inhibitor." The Examiner further contends that the dependent claims are also rejected because they depend from the rejected base claims and are also indefinite as to the nature of the active ingredient in the claimed method.

The relevant inquiry in determining whether a given claim

satisfies the requirements of 35 U.S.C. §112, second paragraph, is whether the claim sets out and circumscribes a particular area with a reasonable degree of precision and particularity such that the metes and bounds of the claimed invention are reasonably clear. In re Moore, 169 U.S.P.Q. 236 (CCPA 1971).

Applicant respectfully submits that the claims, as previously submitted were clear. However, in an effort to eliminate any ambiguity perceived by the Examiner with regard to the terms "PTEN agonists" and "PI-3 kinase," Applicant has amended the claims to recite administering "an effective amount of at least one PI-3 kinase inhibitor" to define the nature of the active ingredient being used.

In light of the foregoing remarks and claim amendments, the above-mentioned rejections under 35 U.S.C. §112, second paragraph cannot be reasonably maintained. Withdrawal of the rejection is respectfully requested.

CLAIMS 91-95, 97-101, 103-107, 109-111, AND 113 AS AMENDED, SATISFY THE WRITTEN DESCRIPTION AND ENABLEMENT REQUIREMENTS OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claims 91-95, 97-101, 103-107, 109-111 and 113 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description and enablement requirements of the statue. Specifically, regarding the written description rejection, the Examiner asserts that the specification does not provide an adequate disclosure of the genus of PTEN agonists, PI3 kinase inhibitors and AKT inhibitors since this genus includes a large number of allegedly unpredictable species. With respect to the enablement rejection, it is the Examiner's view that the specification is enabling for a method of using LY294002 and Wortmannin for effectively inhibiting aberrant tumor-associated angiogenesis, but it allegedly does not reasonably

provide enablement for any other PTEN agonist, PI3 kinase inhibitor, or AKT inhibitor.

Applicant respectfully disagrees with the Examiner's position. However, in the interest of expediting prosecution of the instant application, Applicant has amended the claims to recite that the PI-3 kinase inhibitor is either LY294002 or wortmannin, thereby overcoming the rejections to the claims for inadequate written description and lack of enablement. Indeed, the Examiner acknowledges on page 5 of the Official Action that "[i]t is concluded that applicants [sic] adequately describes LY294002 and wortmannin." Also on page 5 of the Official Action the Examiner states that "the specification, while being enabling for method [sic] using LY294002 and Wortmannin ... does not reasonably provide enablement for any other PTEN agonist, PI3 kinase inhibitor, AKT inhibitor."

Applicant is perplexed, however, with the Examiner's later statement in the second full paragraph of page 6 where it is erroneously stated "[t]he specification fails to provide enablement for the claims drawn to method of using LY294002 and Wortmannin. However, the specification does not provide how to make other PTEN agonist, PI3 or AKT inhibitor." Clearly the Examiner intended to convey that the specification **does** provide enablement for claims using LY294002 and Wortmannin, as evidenced by the statement at page 5, cited above.

Based on the above, the written description and enablement rejections of claims 91-95, 97-101, 103-107, 109-111 and 113 are untenable and Applicant respectfully requests their withdrawal.

CLAIMS 91, 92, 95, 96, 98, 104 AND 110-114, AS AMENDED, ARE NOT ANTICIPATED BY HU ET AL. AS EVIDENCED BY JIANG ET AL.

The Examiner has also rejected claims 91, 92, 95, 96, 98, 104, and 110-114 under 35 U.S.C. §102(a) as allegedly anticipated by Hu et al. as evidenced by Jiang et al. Hu et al. allegedly teach a method of treating cancer comprising administering LY294002 to tumor-bearing mice, which the Examiner contends is the same as "a patient in need thereof," but Hu et al. do not teach the mechanism of action of LY294002 to be inhibiting aberrant tumor-associated angiogenesis. However, it is the Examiner's position that the method of Hu et al. will inherently lead to inhibition of aberrant angiogenesis in tumor cells, and cites Jiang et al. for the mechanism of action of the PI-3 kinase inhibitor.

Applicant respectfully disagrees with the Examiner's position. It is a well-settled premise in patent law that in order to constitute evidence of lack of novelty under 35 U.S.C. §102(b), a prior art reference must identically disclose each and every element of the rejected claim. In re Bond, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Furthermore, the MPEP states at §2131.01(III) that to "serve as an anticipation when the reference is silent about the asserted inherent characteristic, such a gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill." Continental Can C. USA v. Monsanto Co., 20 U.S.P.Q. ed 1746, 1749 (Fed. Cir. 1991). Additionally, as set forth in MPEP §2112(IV), "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993). … Inherency, however, may not be established by probabilities or

possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 49 U.S.P.Q.2d 1949, 1950-51, Fed. Cir. 1999).

The instantly rejected claims recite methods for treating cancer through the administration of a PI-3 kinase inhibitor, wherein the PI-3 kinase inhibitor inhibits aberrant tumor-associated angiogenesis. Hu et al. demonstrate that LY294002 was effective to reduce tumor growth and ascites formation in a nude mouse model of ovarian cancer. Notably, ascites formation is not associated with aberrant angiogenesis. Hu et al. indicate that LY294002 inhibited OVCAR-3 cell (derived from epithelial cells) proliferation directly (see, e.g., Figure 4). Thus, the compound is shown to exert demonstrable, toxic effects directly on the tumor cells themselves. The skilled person is given no suggestion whatsoever that LY294002 affects tumor-associated angiogenesis. Indeed, Hu et al. do not even mention effects on angiogenesis in the two proposed mechanisms of action for the LY294002 compound. At page 884, first column, Hu et al. state that "one possibility is that LY294002 inhibits cell cycle progression. … The second possibility is that LY294002 increases apoptosis of ovarian carcinoma." To anticipate a claim, the reference must teach each and every element of the claim. Hu et al. clearly do not teach each and every element of the claimed invention.

Jiang et al. describe experiments to assess angiogenesis in a growing chick embryo chorioallantoic membrane assay. As such, this reference describes the effect of LY294002 on embryonic angiogenesis, a system which is completely unrelated to tumor formation. Indeed, embryonic angiogenesis is a natural, regulated process of cell signaling which results in maturation of the chick embryo. Jiang et al. perturbed their artificial, *in vitro* system by overexpressing viral oncogenes in an avian retroviral vector in a constitutive fashion. It is this addition of the retroviral oncoproteins that resulted

in aberrant angiogenesis (see, e.g., Figures 1 and 2). Applicant submits that the skilled person, at the time the application was filed, would not view the *in vitro* system of Jiang et al. as "evidence" that *in vivo* administration of a PI-3 kinase inhibitor would have a therapeutic effect on the aberrant angiogenesis observed in *in situ* tumors. Furthermore, no reason is provided that would allow a skilled artisan to extrapolate embryonic angiogenesis to angiogenesis that occurs during occult tumor formation.

Applicant has also added new claims 120 and 121 which recite a positive step of monitoring microvessel density and assessing the inhibition of angiogenesis, respectively, following the administration of the PI-3 kinase inhibitor. Clearly, Hu et al. and Jiang et al. do not disclose such a step and, therefore, fail to teach each and every element of the instantly claimed invention.

In view of the foregoing, Applicants respectfully submit that the rejection of claims 91-92, 95-96, 98, 104, and 110-114 under 35 U.S.C. §102(a) cannot be reasonably maintained. Applicant respectfully requests its withdrawal.

CLAIMS 91, 95, AND 110, AS AMENDED, ARE NOT ANTICIPATED BY SCHULTZ ET AL. AS EVIDENCED BY OIKAWA ET AL.

The Examiner has rejected claims 91, 95 and 110 under 35 U.S.C. §102(b) as allegedly being anticipated by Schultz et al. as evidenced by Oikawa et al. Schultz et al. allegedly teach a method of cancer treatment comprising administration of an effective amount of wortmannin to a patient in need thereof, but do not teach that wortmannin effectively inhibits aberrant tumor-associated angiogenesis. However, the Examiner asserts that Applicant's method is anticipated by Schultz et al. because the method of Schultz et al. will inherently lead to inhibition of aberrant angiogenesis in tumor cells, and cites Oikawa et al. for the mechanism of action and the

teaching that wortmannin is a potent inhibitor of angiogenesis.

Applicant respectfully disagrees with the Examiner's position for reasons similar to those set forth above regarding Hu et al. and Jiang et al. As with Hu et al., Schultz et al. suggest wortmannin effects tumors directly and fail to teach or suggest a role for wortmannin in tumor-associated angiogenesis. Furthermore, it is noteworthy that Schultz et al. conclude that "further studies need to clarify whether a PI3 kinase inhibitor alone is able to completely inhibit tumor cell growth" and that they were "unable to conclude to what extent inhibition of PI3-kinase contributes to the limited antitumor activity of wortmannin" (page 1138).

Additionally, Oikawa et al., like Jiang et al., describe experiments to assess angiogenesis in a growing chick embryo chorioallantoic membrane assay. The results from embryonic angiogenesis are not equated with angiogenesis that occurs during occult tumor formation. Additionally, Oikawa et al. state that "taken together it seems reasonable to speculate that wortmannin influences in vivo angiogenesis through inhibition of phosphotidylinositol 3-kinase, although the possibility that other molecule(s) may be a target cannot be completely excluded, because there is one report suggesting that this microbial product may affect phospholipase A2, at low nanomolar concentrations (Cross et al. 1995). If the above speculation is true..." (page 95). The foregoing disclosure highlights the uncertainty of Oikawa et al. regarding whether wortmannin acted through PI-3 kinase or phospholipase A2. Accordingly, the Examiner's reliance on this reference as "evidence" of anticipation appears misplaced.

In light of the foregoing, the cited references fail to teach each and every element of the instantly claimed methods. Accordingly, Applicant submits that the rejection of claims

91, 95 and 110 under 35 U.S.C. §102(b) is untenable and should be withdrawn.

CLAIMS 91-94 AND 98-100, AS AMENDED, ARE NOT ANTICIPATED BY THE '760 PATENT AS EVIDENCED BY STAMBOLIC ET AL.

The Examiner has rejected claims 91-94 and 98-100 under 35 U.S.C. §102(e) as allegedly anticipated by the '760 patent as evidenced by Stambolic et al. The '760 patent allegedly teaches a method of treating cancer comprising administering TNF-α to inhibit aberrant tumor-associated angiogenesis and the additional chemotherapeutic agent, etoposide, but the '760 patent does not teach that TNF-α is a PTEN agonist. However, the Examiner contends that Applicant's method is anticipated by the '760 patent because the method of the '760 patent will inherently inhibit aberrant tumor-associated angiogenesis, and cites Stambolic et al. for the teaching that TNF-α is a PTEN agonist.

Applicant respectfully disagrees with the Examiner's position. However, as stated hereinabove, claim 91, from which the other claims depend, recites that the at least one PI-3 kinase inhibitor is selected from the group consisting of LY294002 and wortmannin. Inasmuch as the '760 patent fails to teach or suggest the use of either wortmannin or LY294002, the '760 patent does not teach each and every element of the instantly claimed invention.

In view of the amendment to the claims, this rejection cannot be reasonably maintained. Withdrawal of the rejection of claims 91-94 and 98-100 under 35 U.S.C. §102(e) is respectfully requested.

CONCLUSION

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the rejections set forth in the June 4, 2007, Official Action be

withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to call the undersigned at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
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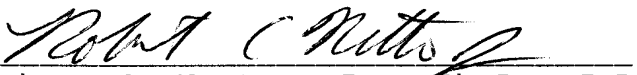
By 
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